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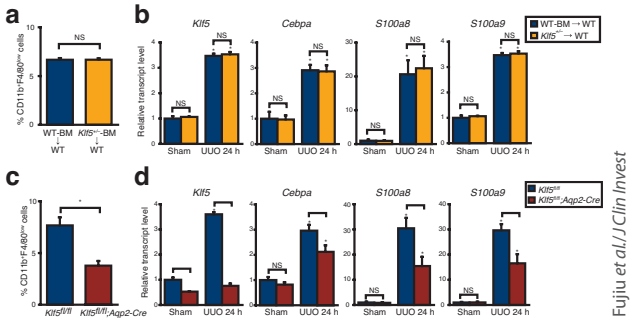
KLF5 arising from the collecting duct is responsible for injury following unilateral ureteral obstruction

Fujiu *et al.*, *J Clin Invest* 2011; **121**: 3425–3441; doi:10.1172/jCI57582



KLF5 in renal collecting duct cells controls renal responses to unilateral ureteral obstruction. (**a** and **b**) Effects of bone marrow (BM)-specific *Klf5* haploinsufficiency on the responses to unilateral ureteral obstruction (UUO). Wild-type mice whose BM had been replaced with either wild-type or $Klf5^{+/-}$ BM were subjected to either UUO or sham operation. (**a**) $CD11b^{+}F4/80^{low}$ fractions were analyzed 24 hours after UUO. $n = 5$. (**b**) mRNA expression 24 hours after UUO. (**c** and **d**) Effects of collecting duct-specific *Klf5* deletion on the response to UUO. $Klf5^{fl/fl}$ and $Klf5^{fl/fl}$;*Aqp2-Cre* mice were subjected to either UUO or sham operation. (**c**) $CD11b^{+}F4/80^{low}$ fractions were analyzed 24 hours after UUO. $n = 5$. $^{*}P < 0.05$. (**d**) mRNA 24 hours after UUO. $^{*}P < 0.05$. NS, not significant.

Tubulointerstitial damage is the final common pathway from chronic kidney disease to end-stage renal disease. Inflammation, as evidenced by the invasion of bone marrow–derived cells and increased cytokine expression, universally accompanies such damage and is thought to be the link between cellular injury and fibrosis. How injury and stress increase fibrosis is of intense interest. Using a unilateral ureteral obstruction model of tubulointerstitial disease, Fujiu *et al.* identified the KLF5 gene product as a key role player in the process. KLF5 is a member of the Krüppel-like transcription factor family, with gene targets that could be engaged in the process of signaling to inflammatory cells and products that determine cell fate. These investigators show that ureteral obstruction upregulates KLF5, primarily in principal cells of the collecting duct, and S100A8 and S100A9, two calcium-binding secretory proteins with potent macrophage-inducing capacities, are transactivated by it within the collecting duct cells. The SA100A8 and SA100A9 gene products emerging from the collecting duct promote macrophage invasion and activation. Engaged macrophages under the influence of these proteins are moved to an M1, or damaging, phenotype and, by disabling the *KLF5* gene in the collecting duct and not in these invading macrophages, ameliorate epithelial injury and the functional decline consequent to obstruction (Figure). Later, other macrophages are activated, this time expressing an M2, or profibrotic, phenotype, and fibrosis proceeds unaffected, and in fact augmented early, by the absence of the *KLF5* gene. Although the authors link the early decline in the M1 macrophage population to the later augmentation of the M2 subpopulation, the arguments put forward are not particularly compelling. Alternate explanations should include the possibility of a separate pathway that initiates fibrosis. That being the case, neither the cellular origin of the signal nor the pathway that executes fibrosis is revealed by the current findings. These observations challenge the supposition that injury begets fibrosis and that the two are inseparable. By dissecting one pathway in great detail, we discover that the two are distinct. These are truly noteworthy observations.

In conclusion, these studies identify the collecting duct as the origin of the injury signal, and a specific macrophage subpopulation produces damage. Fibrosis can be separated from cellular injury. How the *KLF5* gene is activated is left unexplored. But, as in other cases in which clarity brings additional and unexpected complexity, this paper expands the opportunity for research in a new direction to help solve the problem of progression in renal disease.

Robert Safirstein

Dysfunction of fibroblasts of extrarenal origin underlies renal fibrosis and renal anemia in mice

Asada *et al.*, *J Clin Invest* 2011; **121**: 3981–3990; doi:10.1172/JCI57301

In chronic kidney disease, fibroblast dysfunction causes renal fibrosis and anemia. The anemia results from reduced erythropoietin production by renal interstitial fibroblasts and the fibrosis from accumulation of collagen-producing myofibroblasts. The origin of fibroblasts/myofibroblasts remains heavily debated, ranging from postulated epithelial–mesenchymal transition to bone marrow–derived fibrocytes and, recently, to pericyte derivation. Now, Asada *et al.* demonstrate that the majority of erythropoietin-producing fibroblasts originate from migrating neuronal crest cells, labeled as extrarenal cells of myelin protein zero–Cre (*P0-Cre*) lineage, which enter the kidney during embryogenesis. In the diseased kidney, these *P0-Cre* lineage-labeled fibroblasts, but not fibroblasts derived from epithelial–mesenchymal transition, transdifferentiate into myofibroblasts as major contributors to fibrosis, with concomitant loss of erythropoietin production. The attenuated erythropoietin production by myofibroblasts could be restored by neuroprotective agents, which also reduced their profibrotic characteristics. While these studies support yet another origin, the embryonal neural crest, for the fibroblast/myofibroblast, these cells share many characteristics with pericytes, raising the intriguing possibility of their common origin and even identity. Taken together, these findings reveal the pathophysiological roles of *P0-Cre* lineage-labeled fibroblasts in the kidney and establish a novel link between renal fibrosis and renal anemia.

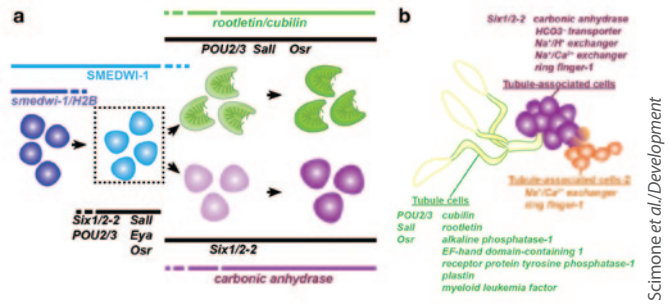
Detlef Schlöndorff

Regeneration of a new excretory system in worms

Scimone *et al.*, *Development* 2011; **138**: 4387–4398; doi:10.1242/dev.068098

The flatworm planarian *Schmidtea mediterranea* has a remarkable regenerative capacity and can fully regenerate from small body fragments. Thus, these animals offer a powerful system for studying the regeneration of cell types, tissues, and even entire organ systems, and for identifying broadly used developmental mechanisms. Scimone *et al.* recently investigated the genetic mechanisms controlling regeneration of the excretory system of these animals, known as protonephridial system, which, as in other animals, regulates waste excretion and osmoregulation. Protonephridia consist of blind tubules that communicate with the outside and end in a terminal cell in which beating cilia generate negative pressure, allowing filtration from the extracellular space into the tubule lumen through membrane fenestrations. Protonephridia are mostly found in small adult animals or larvae of several phyla. Interestingly, in the fly (*Drosophila melanogaster*), the excretory filtration cell, called a nephrocyte, is separated from the Malpighian tubule, and recently, it was found to have remarkable similarities to the vertebrate podocyte. Scimone *et al.* used RNA interference screening and identified a set of genes, *Six1/2-2*, *POU2/3*, *hunchback*, *Eya*, and *Sall*, that encode transcription-regulatory proteins that are required for planarian protonephridia regeneration. During regeneration, planarian stem cells are induced to form a cell population in regeneration blastemas expressing *Six1/2-2*, *POU2/3*, *Eya*, *Sall*, and *Osr* that is required for excretory system formation. *POU2/3* and *Six1/2-2* are essential for these precursor cells to form. Of great interest is that *Eya*, *Six1/2-2*, *Sall*, *Osr*, and *POU2/3*-related genes are required for vertebrate kidney development, showing that planarian and vertebrate excretory cells express homologous proteins involved in reabsorption and waste modification. This detailed analysis of planarian protonephridia identifies a transcriptional program and cellular mechanisms for the regeneration of an excretory organ (summarized in the Figure) and suggests that metazoan excretory systems are regulated by genetic mechanisms that share a common evolutionary origin.

Juan Oliver



Scimone *et al.*/*Development*

A genetic and cellular program for regeneration of the planarian protonephridia. (**a**) Model for protonephridia regeneration: Neoblasts (dark blue, dividing cell expressing *smedwi-1* and *histone H2B*) produce a transient population of precursor cells (light blue) that coexpresses *Six1/2-2*, *Eya*, *Osr*, *POU2/3*, *Sall*, and SMEDWI-1. Some cells expressing *Six1/2-2*, *POU2/3*, and *Sall* expressed neoblast-specific *H2B* (S-phase marker) and/or *smedwi-1* mRNA. The dotted box indicates that data cannot distinguish whether this precursor population is homogeneous or heterogeneous in potential. Precursor cells differentiate either as a tubule cell (green), maintaining expression of *POU2/3*, *Sall*, and *Osr* and expressing *rootletin* and *cubilin*, or as a tubule-associated cell (magenta), maintaining *Six1/2-2* expression and expressing *carbonic anhydrase* (*CA*). (**b**) Schematic of the planarian protonephridial system. Genes expressed in either tubule (green and yellow), tubule-associated cells (magenta), or tubule-associated cells-2 (orange) are shown.

Long interdialytic interval and mortality among patients receiving hemodialysis

Foley *et al.*, *N Engl J Med* 2011; **365**: 1099–1107; doi:10.1056/NEJMoa1103313

Recent trials comparing daily short and nocturnal dialysis have demonstrated benefits of these methods of dialysis delivery over conventional thrice-weekly dialysis in terms of left ventricular geometry and quality of life.[1,2] The observational study by Foley *et al.* further examines how dialysis is delivered and its associations with outcomes. Using the End-Stage Renal Disease Clinical Performance Measures Project, this analysis examines the risk of morbidity and mortality among more than 32,000 patients receiving hemodialysis three times weekly during the period from 2004 to 2007. The mean age of people included in the analysis was 62.2 years, and approximately 25% had received dialysis for less than 1 year at the time of their follow-up. After a mean follow-up of 2.2 years, more than 40% of the cohort died. Mortality rates were highest on the day of the first dialysis treatment of the week and fell on the day following this first treatment to a rate that remained stable for the remainder of the week. This elevated mortality risk on the day following the longest interval was seen primarily among cardiovascular causes of death. A similar trend was noted in hospital admission rates. For any cardiovascular cause, congestive heart failure, and dysrhythmia, the highest risk was noted on the day following the 2-day interval between sessions and followed a zigzag pattern for the rest of the week. In general, the risk of admission was higher on dialysis than on adjacent nondialysis days and trended lower as the week progressed. The trend related to timing of dialysis was reasonably consistent among subgroups, based on demographics and clinical characteristics.

This study supports the studies completed by the Frequent Hemodialysis Network that indicate that the methods or intervals in which dialysis doses are delivered can play a key role in the significant morbidity and mortality of patients on hemodialysis. The application of these findings needs to consider the many complicated features of the delivery of dialysis care, including the ability to provide extra sessions under the current structure of reimbursement.

Lynda Szczech

[1] *Kidney Int* advance online publication, 20 July 2011, doi:10.1038/ki.2011.213. [2] *N Engl J Med* 2010; **363**: 2287–2300.